CASE REPORT

Bilateral chorea/ballismus: detection and management of a rare complication of non-ketotic hyperglycaemia

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SUMMARY

Non-ketotic hyperglycaemia (NKH) is the most common metabolic cause of hemichorea-hemiballismus (HC-HB) and an often-reversible condition. A 68-year-old man presented to the emergency department with a severe hyperglycaemic episode and altered mental status. He was treated appropriately and discharged home after his blood glucose levels were normal with an improvement of mental status. Four weeks after the discharge, he returned with flailing movements of bilateral upper and lower limbs. MRI of the brain revealed hyperintensities of the bilateral putamen on T1-weighted imaging. The patient's symptoms improved with a combination of amantadine, clonazepam and tetrabenazine. Several hypotheses involving gemistocytes, calcification and petechial haemorrhage were proposed in support of imaging abnormalities in the striatum. Dopamine-depleting agents and neuroleptics are used in the treatment of chorea. It is recommended to try a dose of tetrabenazine in patients with NKH-induced HC-HB if no improvement is appreciated with initial treatment of glycaemic control.

BACKGROUND

Chorea/ballismus can be a complication of non-ketotic hyperglycaemia (NKH) in poorly controlled type 2 diabetes mellitus and brain imaging may reveal hyperintense lesions in the striatum. Post-hyperglycaemic manifestations of chorea are usually benign and can be reversed with prompt management of blood glucose levels along with tetrabenazine. The literature contains several cases of NKH-induced hemichorea-hemiballismus (HC-HB) associated with radiological changes of contralateral basal ganglia. However, few describe an associated generalised chorea. We submit a case of type 2 diabetes mellitus who initially presented with NKH secondary to medication non-compliance and developed a generalised chorea-ballismus a few weeks later.

CASE PRESENTATION

We present the case of a 68-year-old man with a known history of type 2 diabetes mellitus, essential hypertension and chronic obstructive pulmonary disorder who presented to the emergency room with confusion and agitation. Vital signs were notable for tachycardia (110 beats per minute), hypertension (180/110 mm Hg) and tachypnoea

(20 breaths per minute). He was afebrile at 37.2°C. His family mentioned that he was non-compliant with his medications. Laboratory tests revealed severe hyperglycaemia (>1160 serum glucose) but no acidosis or ketosis. The patient received intravenous hydration and an insulin drip. A ketone screen was negative. The patient had acute kidney injury from dehydration. Blood glucose levels were normalised by the following day and his mental status improved back to baseline. Education regarding diabetes and medication compliance was given. His home insulin regimen was adjusted, and he was discharged home.

Four weeks discharge, the patient presented to the emergency department again with involuntary, generalised flinging movements. His ballismus started 2 weeks after his initial discharge with a gradual onset and progressively worsening into a large amplitude, flailing movements of bilateral upper and lower limbs, and with an inability to walk. The patient developed rhabdomyolysis likely from the uncontrolled motor activity and subsequently developed AKI. His creatine kinase was more than 16 times the upper limit of normal, though his urine myoglobin level was not tested. The patient displayed no seizure-like activity. He was haemodynamically stable. The laboratory tests of the first and second admissions are in [table 1](#). Of note, he was only mildly hyperglycaemic during this second admission at 200 mg/dL. Cerebrospinal fluid analysis was unremarkable. His head CT showed age-related atrophy and small and large vessel disease. Brain MRI revealed hyperintensities of the bilateral putamen on T1-weighted imaging ([figure 1](#)).

Further investigation revealed negative screen for antinuclear antibodies and paraneoplastic panel as well as for toxoplasmosis, cryptococcus, herpes, Lyme disease and heavy metals including copper, arsenic, mercury, cadmium, cyanide and lead. CT chest, abdomen and pelvis revealed no malignancy. He was started on a combination of amantadine, clonazepam and tetrabenazine with mild clinical improvement but not resolution of the symptoms before the patient was discharged home. A follow-up MRI brain was planned as an outpatient but not performed because the patient died at home for unknown reasons. The family did not request an autopsy.

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Table 1 Laboratory results of the first and second admissions

Laboratory test	Admission 1	Admission 2	Reference range
Haemoglobin	15.5	13.2	13–15 g/dL
RCC	5.76	4.77	4.6–6.8×10 ¹² /L
WCC	13.7	16	3.6–10.3×10 ⁹ /L
Platelets	277	295	140–420×10 ⁹ /L
Blood glucose	>1160	200	70–100 mg/dL
Sodium	120	140	135–145 mmol/L
Potassium	6.8	4.8	3.7–5.1 mmol/L
Chloride	79	103	96–110 mmol/L
Bicarbonate	21	26	22–32 mmol/L
Ketone screen	Neg	Neg	
pH	7.35	7.38	7.35–7.45
Blood urea	36	71	6–24 mg/dL
Creatinine	1.5	2	0.6–1.3 mg/dL
CPK	200	3200	30–200 U/L
HbA1c	13.8%	***	4.3%–6%

The greatly elevated serum glucose level on the first visit, compared with the second visit, as well as high creatine kinase consistent with severe rhabdomyolysis in the second admission.

CPK, Creatine Phosphokinase; HbA1c, haemoglobin A1c; RCC, red cell count; WCC, white cell count.

OUTCOME AND FOLLOW-UP

Patient passed away a few months after the hospitalisation from an unrelated cause.

DISCUSSION

Chorea and ballismus fall under the category of hyperkinetic movement disorders and are due to lesions of the basal ganglia. Rapid, involuntary, non-rhythmic, non-stereotypical, small amplitude movements are termed as chorea, while ballismus is a proximal chorea that produces flinging movements of high amplitude. HC-HB is the involvement of one-half of the body

that occurs due to disinhibition at the level of the contralateral striatum or subthalamic nucleus. Cerebrovascular insults, neoplasms, infections, metabolic disorders, neurodegenerative disorders and immunological diseases are known aetiologies.¹ Poorly controlled diabetes mellitus leading to hyperosmotic, NKH is the most common metabolic cause of HC-HB. NKH-induced HC-HB is a rare, often-reversible condition with a low prevalence. Besides an abnormal metabolic panel, it is associated with noticeable changes in neuroimaging. CT and MRI scans of several affected patients showed hyperdensities and hyperintense signals respectively on the contralateral striatum.² These imaging abnormalities can be found in the caudate or putamen or both.³ The duration of NKH needed for developing HC-HB varies individually. In a study of 20 patients, the mean time of onset for symptoms to manifest was 33 days with a range of 4–180 days.⁴ The overall prognosis of the disease is good. However, the recovery time varies from days to months. Appropriate correction of blood glucose levels with or without antichorea medications is the mainstay of treatment.²

Epidemiology

NKH-induced chorea was first reported in 1960.⁵ Since then, many similar cases have been reported in the literature, and several studies are being done to trace its pathophysiology. Choreiform movements are usually seen after NKH episodes in previously known patients with diabetes. However, some reports noted the involuntary movements being the presenting symptoms of diabetes without a previous history of hyperglycaemic episodes.⁶ These abnormal involuntary movements often develop subacutely and gradually worsen over few weeks.⁴ Although NKH usually presents as HC-HB, some cases were reported to be generalised chorea. A meta-analysis of 53 cases conducted by Oh *et al*² showed that 89% of the cases had haemichorea with contralateral putaminal hyperintensity and 11% had generalised chorea with bilateral putaminal changes on MRI. The estimated prevalence of this disorder is less than 1 in 1 000 000. It is more common in elderly women with the mean age of onset being 71 years.² Asian ethnicity is found to be more commonly associated with NKH-induced HC-HB, but cases have also been reported in other ethnic groups worldwide.⁴

Pathophysiology

The pathophysiology of NKH-induced chorea is not clearly understood, with several competing hypotheses. Gamma-aminobutyric acid (GABA) antagonists are known to cause involuntary movements in animal models,⁷ indicating the importance of decreased GABA levels in the pathogenesis of HC-HB. In NKH, aerobic metabolism is shifted to anaerobic processes, and GABA is used as an alternative substrate. A reduced GABA level leads to loss of inhibition at thalamus, which in turn causes hyperactivation of dopaminergic neurons and initiation of involuntary movements.⁸ This also might explain the reason for HC-HB being more commonly associated with NKH than in ketosis, as the latter process replaces the levels of decreased GABA. A positron emission tomography scanning in three patients with NKH showed decreased glucose metabolism in the areas corresponding to the neuroimaging abnormalities, suggesting hyperglycaemia and vascular insufficiency as the major contributors for the metabolic derangement.⁹ Increased osmolarity due to NKH could be responsible for the blood–brain barrier disruption leading to vascular insufficiency¹⁰ which could be a possible pathogenesis for a generalised or a haemichorea in NKH. A single-photon emission CT study conducted in six patients with NKH (five

Figure 1 Hyperintense lesions of the bilateral putamen on T1-weighted MRI. PF, Posterior Fossa.

haemichorea and one generalised chorea), showed decreased perfusion in the contralateral striatum in all cases suggesting decreased blood supply as a possible pathology.¹¹ The neuroimaging findings, however, do not support the above said. Several hypotheses involving gemistocytes, calcification and petechial haemorrhage were proposed in support of imaging abnormalities in the striatum, of which gemistocyte explanation appears to be most probable one. Gemistocytes are the reactive swollen astrocytes during the acute injury that gradually shrink with the improvement of the critical condition. Some pathological studies have confirmed the presence of these cells in the putamen of patients with choreic NKH.^{12–13} The hydrated protein layer in these bulging cells would probably be the reason for shortening of T1 relaxation and high intensity on MRI.¹⁴

Non ketotic hyperglycemic chorea-ballismus shows restricted diffusion on DWI and variable but generally hypointense on T2 sequences. However, the T1 hyperintensities in basal ganglia, particularly in the putamen and caudate, are the most prominent, typical and helpful. These findings gradually resolve with glycaemic correction. The discovery of T1-weighted hyperintensities in basal ganglia in this patient should prompt an investigation for metabolic causes such as hepatic failure causing copper accumulation and pseudohypoparathyroidism, ruling out manganese toxicity if work-related exposure is possibility. Also, in the differential is early-late subacute haemorrhage, especially in a patient with diabetes with vascular risk factors, and calcifications if the above are unlikely.¹⁵ The region involved with the petechial haemorrhage is most likely in the indirect pathway, which does not match with the hyperintense areas, and lack of disappearance of calcifications on the CT-scans in some patients suggests both calcifications and haemorrhage as a less possible reason for MRI changes.¹³ Also, the absence of the calcification and petechial haemorrhage on the autopsy of an NKH-induced HC-HB supports the above said.¹²

Prognosis

Posthyperglycaemic manifestations of chorea are usually benign. The prognosis depends on the level of proper glycaemic control in a patient with diabetes and prompt diagnosis in undiagnosed diabetic individuals. The average time for the resolution of symptoms with medical management is 2 weeks. However, resolution of abnormal findings on CT/MRI may take several months.⁴

Management

Prompt restoration of serum glucose to the basal level is the mainstay in treating NKH-induced HC-HB. The vast majority of cases do not require any additional management besides glycaemic control and symptoms are usually reversible. Apart from this, neuroleptics and dopamine-depleting agents have been the most widely used agents in the treatment of chorea. Neuroleptics act by blocking dopamine receptors. Olanzapine and risperidone are commonly used neuroleptics in chorea among patients with Huntington's disease.¹⁶ Huntington's chorea is usually treated with a dopamine depletor like tetrabenazine, along with the newer deutetabenazine and valbenazine are for the same indication including tardive dyskinesia and hemiballismus.¹⁷ However, their benefits in NKH-induced chorea have been seldom reported. Tetrabenazine prevents the release of monoamines by inhibiting vesicular monoamine transporter 2. Additionally, it has a mild dopamine receptor blocking property.¹⁸ Umeh *et al* reported a 65-year-old man with diabetes and HC-HB who showed a dramatic improvement in the symptoms on tetrabenazine. Also, the patient's symptoms

worsened on stopping the medication.¹⁹ Another reported case in the literature is of a newly diagnosed diabetic with HC-HB showing a dramatic response to tetrabenazine.¹⁸ For cases that do not respond to hyperglycaemic control alone, it would be reasonable to try tetrabenazine in patients with NKH-induced HC-HB.

Generalised chorea cases can be secondary to multiple causes and the differential diagnosis expands to drug-induced, hereditary and acquired causes. The chorea often improves with treatment of the underlying symptom, but in many cases the same agents used to treat primary choreic movements can be applied to motor symptoms of secondary chorea. It is important to distinguish carefully the movements characterising a Wilson's disease from a Sydenham's chorea or a levodopa-induced chorea as the management is different, such that training to recognise such movement disorders would be of great benefit. Aside from the effective agents described before, there is clinical evidence supporting an antichorea effect with benzodiazepines²⁰ and less so for valproic acid, carbamazepine, oxcarbazepine, topiramate, levetiracetam and gabapentin.^{21–22} Pallidotomy, thalamotomy and deep brain stimulation have been reported to help reduce chorea for multiple aetiologies, but consideration for surgery should be taken carefully and only if patients lack cognitive abnormalities.^{23–24}

Learning points

- ▶ Chorea/ballismus can be a complication of non-ketotic hyperglycaemia in poorly controlled type 2 diabetes mellitus.
- ▶ Striatal hyperintense lesions on brain MRI can support the diagnosis.
- ▶ It is recommended to try a dose of tetrabenazine in patients with non-ketotic hyperglycaemia-induced chorea/ballismus.
- ▶ It is important to consider a broad differential for a generalised case of chorea.
- ▶ The treatment for secondary chorea is often the same as with primary aetiologies.

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